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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/577,489	WOOD ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-40,42-44 and 51-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-40,42-44 and 51-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 28-40, 42-44, and 51-59 are pending. Applicants previously cancelled claims 1-27, 41, and 46. Applicants have newly cancelled claims 45 and 47-50. Applicants have amended claims 28 and 44. Receipt and consideration of Applicants' amended claim set and remarks/arguments submitted on September 10, 2007 are acknowledged. Applicants are advised that the examination of the instant application is being conducted by a new examiner.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/10/2007 has been entered.

Moot Rejections/objections

All rejections and/or objections of claims 45 and 47-50 cited in the previous office action mailed on February 7, 2007 **are moot**, because said claims have been cancelled.

Specification

Claim 44 is objected to because of the following informalities: the word "is" is repeated twice consecutively in lines 1-2. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 42-43 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 28-40, 42-45, and 47-59 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is maintained** for the reasons of record and further articulated below.

Response to Arguments

Applicant's arguments filed September 10, 2007 have been fully considered but they are not persuasive. Applicants have traversed this rejection by asserting that adequate written support for the claimed method is provided on page 3, lines 21-24 of the instant specification. The Examiner respectfully disagrees, because said cited portion of the specification merely states

that Applicants' invention is particularly useful for the treatment of specific diseases (i.e. asthma, emphysema, respiratory distress syndrome, chronic bronchitis, cystic fibrosis, AIDS, and AIDS related pneumonia). Although this may satisfy the utility requirement, it is insufficient to describe the claimed invention, because there is no mention of the specific required steps in the instant specification. Applicants' examples described methods of nebulizing aqueous suspensions of crystalline beclomethasone dipropionate (BDP) with a particle size distribution (PSD) of **0.26 ± 0.13 mm** (Example 1) and an aqueous suspension of a contrast agent (WIN 68209) (Example 2), but these do not describe a method of treating a specific disease by administration to a mammal's lungs. It is noted that Applicants' claims require that the suspended crystalline particles have a size of less than 400 nm, however, a PSD of **0.26 ± 0.13 mm** is several orders of magnitude greater than what is claimed.

Furthermore, it is noted that Applicants have indicated that suitable therapeutic agents include "blood products and substitutes." However, a search of the prior art did not uncover any recognition in the art that one can crystallize red blood cells, white blood cells, blood plasma. Applicants do not provide a description of how one can crystallize red blood cells, white blood cells, and blood plasma; thus it is concluded that Applicants were not in possession of the claimed method as it pertains to suspended crystalline "blood products and substitutes." It is also noted that several blood proteins, such as human Factor IX, were not reported crystallized until after Applicants' effective filing date of February 24, 1995 (See Huang, M. et al. "Crystal Structure of the Calcium-Stabilized Human Factor IX Gla Domain Bound to a Conformation-specific Anti-Factor IX Antibody" *The Journal of Biological Chemistry*, **2004**, *279(14)*, pp 14338-14346). As a result, it is doubtful that Applicants were in possession of all blood products

in crystalline form suspended in an aqueous formulation. Common "blood substitutes" are perfluorocarbons, which are not solids at physiological (e.g. 37 °C for humans) and ambient temperatures (e.g. 25 °C), but rather liquids. Applicants have not described how to obtain crystalline perfluorocarbons, thus, it is concluded that Applicants were not in possession of aqueous suspensions of perfluorocarbons as of the effective filing date of February 24, 1995. With regard to the treatment of respiratory diseases, it is noted that many of the drug types recited in claim 37 are not art recognized as being suitable for the treatment of any respiratory disease, let alone the specific respiratory diseases mentioned in Applicants specification, such as asthma and cystic fibrosis. For example, anthelmintics (e.g. Albendazole) are used to treat worm and parasite infestations; antiepileptics (e.g. TEGRETOL) are used to treat seizure and are not indicated for the treatment of any respiratory disease, let alone asthma, cystic fibrosis, respiratory distress syndrome, emphysema, and chronic bronchitis. In summary, the instantly claimed method of treatment is deemed to lack adequate written description in the instant specification.

Claims 28-37, 39-40, 42-45, and 47-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of a respiratory illness selected from the group consisting of asthma, cystic fibrosis, emphysema, chronic bronchitis, and respiratory distress syndrome by administration to the lungs of a mammal of an aqueous suspension of crystalline beclomethasone, does not reasonably provide enablement for the treatment of any respiratory disease with any drug (e.g. blood products, anxiolytics, muscle relaxants) delivered in the form of an aqueous suspension of crystalline drug to said mammals lungs. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad. Applicants are claiming the treatment of any respiratory disease by the administration to the lungs of any mammal of an aqueous suspension of any crystalline therapeutic agent. Applicants' claims also read on the administration of single crystalline unit cell of a single molecule with a size of a few (e.g. 1-3) nanometers.

Nature of the invention/State of the (Prior/Post) Art

The instant invention is drawn to a method of treating any respiratory disease in any mammal by the administration to the lungs of said mammal of an aqueous suspension of any crystalline therapeutic agent in droplets with a size of less than 10 microns, wherein the suspended therapeutic agent has a submicron size (e.g. less than 400 nanometers). The art does not recognize that analgesics, anthelmintics, ant-arrhythmic agents, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihypertensive agents, immunosuppressants, antithyroid agents, anxiolytic sedatives, blood products and substitutes, cardiac inotropic agents, diuretics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parathyroid calcitonin and biphosphonates, prostaglandins, sex hormones, stimulants (e.g. caffeine), anorectics, sympathomimetics, thyroid agents, or xanthines are indicated for the treatment of any respiratory diseases (See Merck Manual Home Edition Articles entitled: "Asthma," "Bronchitis", "Cystic Fibrosis", and "Respiratory Distress Syndrome"). The art recognizes the anti-inflammatory corticosteroids (e.g. beclomethasone) are suitable for the treatment of some symptoms of asthma, bronchitis, cystic fibrosis, emphysema, and respiratory distress syndrome (See cited Merck articles).

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970).

Guidance/Working Examples

Applicants' specification provides no guidance or working examples concerning the claimed method of treating any respiratory disease in any mammal by the administration to the lungs of said mammal of any crystalline therapeutic suspended in an aqueous formulation. It would require an undue burden upon an ordinary skilled artisan to ascertain which of the thousands or millions of crystalline therapeutic agents are suitable for the treatment of any respiratory condition in any mammal, such as clinical trials involving hundreds or thousands of individuals. For example, the treatment of asthma by the administration of antiepileptics is unknown and Applicants have provided no data or guidance indicating which antiepileptics are suitable for the treatment of asthma, what dosages and dosing regimens are necessary for treating asthma with antiepileptics, and how said dosages/dosing regimens would vary from one mammalian species to another or even between genders and different age groups (e.g. adults vs. juveniles) of a given mammalian species. The mere suggestion that a given composition may be suitable for treatment of a few respiratory diseases is insufficient guidance as to how to effectively treat all respiratory disease with any crystalline therapeutic agent. It is also noted that Applicants provide no direction as how to administer a single crystalline unit cell having a size of a few nanometers suspended in water to a mammal's lungs. In conclusion, Applicants' specification is enabling for the treatment of a respiratory illness selected from the group consisting of asthma, cystic fibrosis, emphysema, chronic bronchitis, and respiratory distress syndrome by administration to the lungs of a mammal of an aqueous suspension of crystalline beclomethasone, does not reasonably provide enablement for the treatment of any respiratory

disease with any drug (e.g. blood products, anxiolytics, muscle relaxants) delivered in the form of an aqueous suspension of crystalline drug to said mammals lungs.

To emphasize this point the Examiner points Applicants to "Genentech, 108 F.3d at 1366 and *Brenner v. Manson,* 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)" which states,

> "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-31 and 51-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29-31 and 51-59 are indefinite because these claims particle sizes of "less than about" a particular numerical value." The phrase "less than about" is indefinite, because it simultaneously claims two different ranges. An ordinary skilled artisan would be unable to ascertain whether the required particle size of a suspended crystalline therapeutic agent is less than 400 nm, for example, or about 400 nm. Appropriate correction is required.

Claim 32 is indefinite regarding what constitutes a polyoxyethylene castor oil derivative, because said derivative is not defined as to its metes and bounds in the specification. The 10th edition of the Merriam-Webster's Collegiate Dictionary (Merriam-Webster Incorporated: Springfield, Massachusetts, 1993, pp 311) defines "derivative" as, "a chemical substance related

structurally to another substance and theoretically derivable from it." For example, carbon dioxide could theoretically be derived from the combustion of polyoxyethylene castor oil. Therefore, the definition of derivative in the Merriam-Webster Collegiate Dictionary does not shed light on what Applicants' intended for the meaning of a polyoxyethylene castor oil derivative.

Claims 42-43 provides for the use of a jet nebulizer (claim 42) or an ultrasonic nebulizer (claim 43) to form an aerosol, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 37 is confusing because it is unclear how both antithyroid agents and thyroid agents are both suitable for the treatment of the same mammalian respiratory disease.

The remaining claims are rejected as depending from a rejected claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-31, 33-49, and 51-59 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 24-30 of U.S. Patent No. 6,264,922 (USPN '922). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of USPN '922 encompass the cited claims of the instant application. Independent claim 28 of the instant application claims a method of treating a respiratory disease by administering to a mammal's lungs aqueous droplets with a size of less than 10 microns having suspended therein or thereon crystalline therapeutic agent with a submicron particle size, wherein said therapeutic agent has at least one surface modifier on adsorbed on the surface of the crystalline therapeutic agent. Independent claim 24 of USPN '922 claims a method of treating a mammal in need comprising delivering nanoparticles dispersed in liquid droplets having a size of less than 10 microns to the lungs of a mammal, wherein (i) the liquid droplets consist essentially of a liquid, crystalline therapeutic agent, and at least one surface modifier and (ii) said nanoparticles consist essentially of (a) crystalline particles of a therapeutic agent that is poorly soluble in said liquid with an effective average particle size of less than 1,000 nm and (b) about 0.1-90% w/w of at least one surface modifier. Dependent claim 30 of USPN '922 indicates that the liquid may be water. Claim 8 indicates that the inventors of USPN '922 contemplated that the nanoparticles could be beclomethasone dipropionate, which is an art-recognized anti-inflammatory corticosteroid indicated for the

treatment of respiratory diseases such as asthma. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-31, 33-49, and 51-59 prima *facie* obvious over claims 8 and 24-30 of U.S. Patent No. 6,264,922 (USPN '922).

Claims 28-31, 33-49, and 51-59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-7 of copending Application No. 11/592,262 (copending '262). Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of both applications are substantially overlapping in scope and mutually obvious. Independent claim 28 of the instant application has been described above in the instant office action. Independent claim 1 of copending '262 claims a method of treating a mammal by administering to the lungs of said mammal an aqueous dispersion of insoluble nanoparticles of a therapeutic agent having a surface modifier on the surface thereof. Dependent claim 7 indicates that the therapeutic agent is beclomethasone, which is an art-recognized anti-inflammatory corticosteroid conventionally used in the treatment of asthma. The term "nanoparticles" reads on the particle size ranges recited in Applicants' claims for the crystalline therapeutic agent. The claims of copending '262 are silent as to the amount of active agent and surface modifier, and thus encompass all conceivable amounts. It would have been with the skill of the ordinary artisan to select appropriate amounts of therapeutic agent and surface modifier. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-31, 33-49, and 51-59 prima *facie* obvious over claims 5-7 of copending Application No. 11/592,262 (copending '262).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 28-40, 42-44, and 51-59 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo

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PRIMARY EXAMINER